UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,792	02/27/2004	Deepa Eveleigh	5152	8120

35969 7590 03/20/2007

JEFFREY M. GREENMAN
BAYER PHARMACEUTICALS CORPORATION
400 MORGAN LANE
WEST HAVEN, CT 06516

EXAMINER	
SCHLAPKOHL, WALTER	
ART UNIT	PAPER NUMBER
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/788,792	EVELEIGH ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *3 and 6-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/31/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the papers filed 11/08/2006. Claims 1-14 are pending. Claims 3 and 6-14 are withdrawn. Claims 1-2 and 4-5 are under examination in the instant Office action.

Election/Restrictions

Applicant's election of Group I (claims 2 and 5) in the reply filed on 11/8/2006 is acknowledged, as is Applicant's election of the combination of SEQ ID NOS:1 and 44. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 3 and 6-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/8/2006.

This restriction is still deemed proper as is therefore made FINAL.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 199(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/450,655, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, provisional application 60/450,655 does not disclose SEQ ID NOS: 1 and 44. Therefore, claims 2 and 5 are only granted benefit of priority to the filing date of the instant application: 2/27/2004.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see, e.g., page 42, lines 20). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The use of the trademark names have been noted in this application (see, e.g., page 22, paragraph [119]). They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 4-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art, the amount of experimentation necessary and the relative skill levels of those in the art. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: The instant claims are drawn to methods of diagnosing breast cancer and methods of distinguishing between normal and disease tissue by comparing the level of expression of one or more genes or gene products between two biological samples. Some claims are further limited to such methods wherein the genes consisting of SEQ ID NO:1 and SEQ ID NO:44. The invention is complex in that it involves measuring a change in the level of gene expression from

practically any two different samples such that any disease can be dinstinguished and/or such that breast cancer can be diagnosed. At a minimum, the nature of the invention requires knowledge of a correlation between the expression of SEQ ID NOS:1 and 44 in a breast tissue sample and the presence of or predisposition to breast cancer.

Breadth of the claims: The claims are extremely broad in that they encompass the use of any diseased biological sample and any normal biological sample, as well as the use of any gene or combination of genes, such that a comparison in the expression of said genes is indicative of any diseased state. With regard to claim 1, the claims are extremely broad in that they encompass diagnosing breast cancer or a predisposition to breast cancer in any patient, and a comparison of gene expression levels for any gene or combination of genes, such that the gene expression level comparison between two samples is diagnostic of the disease. The large breadth of the claims exacerbates the complexity of the invention.

Guidance of the specification/The existence of working examples: The specification teaches the results of a microarray experiment performed with cRNA samples from human breast tissue and normal adjacent tissue purchased from the National Disease Research Institute (see Example, 1, pages 41-43). Three marker

sets were obtained as a result, the first was obtained by subjecting the data to a t-test and collecting the data for a probe set which showed a p-value of less than or equal to 0.001 (see page 42, paragraph [199]). The data were then further selected by a Perl program "to select subsets of the data and feed these sets to svm-train for training support vector machines (SVM)" (ibid). Marker Set Two was obtained similarly, only the data set was not limited to those probe sets that showed a t-test p-value of less than or equal to 0.001 (page 43, paragraph [200]). Marker Set Three, which consists of two sequences (SEQ ID NOS:1 and 44), "represents a set of probe sets that is an optimum set for the prediction of whether or not a tissue is cancerous using the Naïve Bayes method" (page 43, paragraph [201]). The specification also teaches that "[a]ll three marker sets could select which tissues were cancerous and which were normal with 100% accuracy using their respective methods as determined by ten fold cross validation" (page 43, paragraph [202]).

The specification does not indicate how many samples were tested nor does the specification provide any guidance as to which samples (diseased or otherwise) can be used in the claimed methods.

The specification does not differentiate or teach how to differentiate the use of differences in expression level of any gene or group of genes such that the comparison is indicative of a disease state in diseased tissue or such that the comparison is diagnostic of breast cancer.

Even for claims that recite the combination of SEQ ID NOS:1 and 44, the specification does not teach what differences in expression levels are required such that differences in expression of the genes of the marker sets are 1) either indicative of any disease state or 2) diagnostic of breast cancer.

State of the prior art: The literature reports the use of SEQ ID NO:1 and SEQ ID NO:44 in methods other than breast cancer diagnosis. Khawaja et al (US Patent Application Publication No. US 2004/0241737 A1) teach the use of CRMP2 (SEQ ID NO:1) in a method of diagnosing mood disorder (see entire documents, especially the Abstract; page 2, paragraph [0013]; and Khawaja et al's SEQ ID NO:5). Jazaeri et al (US Patent Application Publication No. US 2005/0095592 A1) teach the use of SGCE as a biomarker for ovarian cancer (see entire document, especially page 48, Table 4, bottom). The prior art also teaches examples of methods wherein a comparison of expression levels of one or more genes is used to either diagnose breast cancer and/or

distinguish a disease state. However, there are no examples in the literature which teach the use of expression levels of SEQ ID NOS:1 and 44 to diagnose breast cancer and/or to distinguish a disease state in any tissue. Thus, the state of the art is silent with respect to the use of SEQ ID NOS:1 and 44 to diagnose the presence of a breast cancer or a predisposition to a breast cancer in particular.

Predictability of the art/Amount of experimentation necessary: The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art by Wu (*J. Pathol.* **195**(1):53-65, 2001.). Wu teaches that gene expression data must be interpreted in the context of other biological knowledge, involving various types of "post genomics" informatics, including gene networks, gene pathways, and gene ontologies (page 53, left column). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (page 63 - Discussion). Additionally, post-filing art reveals that most gene association studies are typically wrong.

Lucentini (The Scientist, page 20, Dec. 20, 2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revised statistical methods should be included in the gene association studies (middle column, 1st full paragraph).

The lack of predictive success of gene expression studies may, in part, be due to the fact that increased mRNA is not always indicative of protein expression levels. Chen et al (Molecular and Cellular Proteomics 1:304-313, 2002) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (page 304) and "it is not possible to predict overall protein expression

levels based on average mRNA abundance in lung cancer samples" (pages 311-312).

Given the complex nature of the invention and the underdeveloped state of the art at the time of filing, there would be a large and prohibitive amount of experimentation required to make and use the claimed invention. Even for claims specifically reciting SEQ ID NOS:1 and 44, one would have to establish whether increased or decreased levels of expression between normal and diseased tissue were indicative of breast cancer or any other disease in a statistically significant manner. Once it was determined whether increases or decreases in SEQ ID NOS:1 and 44 were indicate of a given disease and/or diagnostic of breast cancer, one would need to perform an analysis of the different levels of expression in a large number of individuals to establish what level of difference in gene expression is considered indicative of a given disease and/or diagnostic of breast cancer. One would then have to establish that those differences in expression are correlated with the presence of a breast cancer or other disease and then further perform studies that such *correlative* expression levels are *predictive* of any given disease tissue and/or diagnostic of breast cancer or any kind.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 4-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a methods of diagnosing breast cancer and methods of distinguishing between normal and disease tissue by comparing the level of expression of one or more genes or gene products between two biological samples. Some claims are further limited to such methods wherein the genes are selected from the groups consisting of SEQ ID NO:1 and SEQ ID NO:44. The claims encompass any disease and any gene or combination of genes such that a comparison of the expression level of said genes in two biological or tissue samples is either indicative of a disease state in the tissue and/or

diagnostic of breast cancer. The claims do not provide any structural information with regard to the gene sequences and/or biological samples capable use in such methods such that any disease state (including breast cancer) can be diagnosed or distinguished. Thus, the rejected claims comprise a set of nucleic acid sequences and biological samples that are defined by their function in the method.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification teaches the results of a microarray experiment performed with cRNA samples from human breast tissue and normal adjacent tissue purchased from the National Disease Research Institute (see Example, 1, pages 41-43). Three marker sets were obtained as a result, the first by subjecting the data to a t-test and collecting the data for a probe set which showed a p-value of less than or equal to 0.001 (see page 42, paragraph [199]). The data were then further selected by a Perl program "to select subsets of the data and feed these sets to svm-train for

training support vector machines (SVM)" (ibid). Marker Set Two was obtained similarly, only the data set was not limited to those probes sets that showed a t-test p-value of ≤ 0.001 (page 43, paragraph [200]). Marker Set Three, which consists of two sequences (SEQ ID NOS:1 and 44), "represents a set of probe sets that is an optimum set for the prediction of whether or not a tissue is cancerous using the Naïve Bayes method" (page 43, paragraph [201]). The specification also teaches that "[a]ll three marker sets could select which tissues were cancerous and which were normal with 100% accuracy using their respective methods as determined by ten fold cross validation" (page 43, paragraph [202]).

No description is provided of a single gene sequence or combination of gene sequences that could be used to indicate whether or not any tissue sample was diseased.

No description is provided of the samples used other than the statement that samples from human breast tissue and normal adjacent tissue were purchased from the National Disease Research Institute.

No guidance is provided for one of ordinary skill in the art to know which genes could be used in combination with which diseases and which biological samples such that breast cancer

could be diagnosed or the presence of any diseased state in a tissue would be indicated.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of three nucleic acid sequence sets capable of indicating whether known breast cancer tissue was of a diseased state. The results are not necessarily predictive of any other genes capable of diagnosing breast cancer and/or any other genes capable of indicated a diseased state. Even in the case where the claims are limited to the combination of SEQ ID NO:1 and SEQ ID NO:44, the results are not predictive of a breast cancer diagnosis from any biological sample from any patient and any biological sample from any normal patient. Thus, it is impossible to extrapolate from the example described herein those nucleic acid molecules used in combination with those biological samples and those diseased tissues such that the genes and samples would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of genes that can be used to diagnose breast cancer from any given patient sample and from any given normal sample. Neither does

the prior art teach the comparison in expression level(s) of any given gene or set of genes in combination with any disease tissue and normal tissue, such that the comparison is necessarily indicative of a diseased state. The literature reports the use of SEQ ID NO:1 and SEQ ID NO:44 in methods other than breast cancer diagnosis. Khawaja et al (US Patent Application Publication No. US 2004/0241737 A1) teach the use of CRMP2 (SEQ ID NO:1) in method of diagnosing mood disorder (see entire documents, especially the Abstract; page 2, paragraph [0013]; and Khawaja et al's SEQ ID NO:5). Jazaeri et al (US Patent Application Publication No. US 2005/0095592 A1) teach the use of SGCE as a biomarker for ovarian cancer (see entire document, especially page 48, Table 4, bottom). However, the literature does not report the use of SEQ ID NOS:1 and 44 (much less any gene or combination of genes) such that they can be used to determine any disease state.

Given the very large genus of nucleic acid molecules encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to the nucleic acid sequences and biological samples capable of fulfilling the claim limitations of claims 1-2 and 4-5, the skilled artisan would not have been able to describe the broadly claimed genus of nucleic acid sequences used in

combination with any patient/diseased sample and or any normal sample, such the a comparison of the expression levels of the nucleic acids is either 1) indicative of a diseased state and/or 2) diagnostic of breast cancer. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those nucleic acid sequences used in combination with those biological samples that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded Applicant was not in possession of the claimed invention for claims 1-2 and 4-5.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by An et al (US Patent No. 6,218,529)

An et al teach a method for providing a patient diagnosis for breast cancer, comprising the steps of (a) determining the level of one or more genes (SEQ ID NO:3) in a biological sample taken from the patient; (b) determining the level of expression of one or more genes in a normal patient sample; and (c) comparing the level of expression of the genes such that a change in the level of expression in the first biological sample compared to the second biological sample is a diagnosis of the disease (see entire document, especially column 5, lines 1-15; column 10; lines 26-29; column 11, lines 1-4 and 25-67; Figure 15; column 72, lines 35-67; and column 73, lines 22-26). An et al also teach such a method wherein the level of expression of one or more genes from a disease tissue and the level of expression of one or more genes from a normal tissue are compared and wherein the comparison is indicative of a disease state (ibid and column 42, lines 37-59).

It is noted that this Office action contains rejections of the same claims under 35 U.S.C. 112, 1st paragraph (enablement) and 35 U.S.C. 102(b). While these rejections may seem contradictory, they are not because each is based upon a different legal analysis, i.e. sufficiency of the disclosure of the instant application to support claims under 35 U.S.C. 112,

1st paragraph vs. sufficiency of a prior art disclosure to anticipate or render obvious an embodiment of the claimed invention (See *In re Hafner*, 161 USPQ 783 (CCPA 1969)).

Conclusion

No claim is allowed.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the

problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent applications to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at (800) 786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

March 12, 2007

DAVID GUZO
PRIMARY EXAMINER